IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
Inventor: Steven M. Dubinett et al.	)	Examiner: Susan Ungar
	)	
Serial #: 10/756,101	)	Group Art Unit: 1642
	)	
Filed: January 13, 2004	)	Appeal No.: _____
	)	
Title: METHODS OF USING SECONDARY LYMPHOID ORGAN CHEMOKINE TO MODULATE PHYSIOLOGICAL PROCESSES IN MAMMALS	)	

BRIEF OF APPELLANTS

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In accordance with 37 CFR §41.37, Appellants hereby submit the Appellants' Brief on Appeal from the final rejection in the above-identified application, as set forth in the Office Action dated September 20, 2007.

Please charge the amount of $510 to cover the required fee for filing this Appeal Brief as set forth under 37 CFR §41.37(a)(2) and 37 CFR §41.20(b)(2) to Deposit Account No. 50-0494 of Gates & Cooper LLP. Also, please charge any additional fees or credit any overpayments to Deposit Account No. 50-0494.

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I. REAL PARTY IN INTEREST

The real party in interest is The Regents of the University of California, the assignee of the present application.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences for the above-referenced patent application.

III. STATUS OF CLAIMS

Claim 32 is pending in the application. Claim 32 was rejected under 35 U.S.C. §103(a) as being obvious in view of a combination of WO/038706 or WO 96/06169 and Kirk et al., Human Gene Therapy, 2000, 11: 797-806 (Kirk), Nishioka et al., Cancer Research, 1999, 59: 4035-4041 (Nishioka), Miller et al., Human Gene Therapy, 2000 (Millet), 11: 53-65 and Lode et al., "Drugs Today 2000, 36:321-336" (Lode), and these rejections are being appealed.

IV. STATUS OF AMENDMENTS

No amendments to the claims have been made subsequent to the final Office Action.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Briefly, Appellants' invention as recited in independent claim 32 is generally directed to a method of attracting T lymphocyte or mature host dendritic cells to a site of a syngeneic tumor in a mammal. This method comprises the steps of obtaining dendritic cells from the mammal, introducing an exogenous polynucleotide encoding the secondary lymphoid tissue chemokine ("SLC") of SEQ ID NO: 1 into the dendritic cells so that SLC is expressed in these cells; and then placing these dendritic cells at the site of the syngeneic tumor in the mammal. In this method, the SLC expressed by these dendritic cells then functions to attract T lymphocyte or mature host dendritic cells to the site of the syngeneic tumor in the mammal.

Referring to the specification by page and line number for the disclosure of this subject matter, see, e.g.: the SLC polypeptide sequence as disclosed at page 64, lines 24-26 (SEQ ID NO: 1), methods such as those disclosed at page 57, lines 2-21, and EXAMPLE 10 at pages 80-81.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claim 32 is unpatentable under 35 U.S.C. § 103(a) as being rendered obvious over a combination of WO/038706 or WO 96/06169 and Kirk et al., Human Gene Therapy, 2000, 11: 797-806 (Kirk), Nishioka et al., Cancer Research, 1999, 59: 4035-4041 (Nishioka), Miller et al., Human Gene Therapy, 2000 (Miller), 11: 53-65 and Lode et al., "Drugs Today 2000, 36:321-336" (Lode).

VII. ARGUMENT

A. Appellants' Specification Provides The First Demonstration of SLC Activity in a Syngeneic Cancer

As noted for example in the paragraph bridging pages 1-2, an understanding of the immune mechanisms that influence oncogenesis, cancer regression, recurrence and metastasis is a crucial aspect of the development of new immunotherapies. In particular, artisans understand that a fundamental aspect of an immune response is the ability of an organism's immune cells to distinguish between self and non-self antigens. Consequently, clinically relevant models which seek to dissect immune mechanisms in cancer must take into account the fact that tumor cells share a genetic background with cells of the host immune system (i.e. are syngeneic). Unfortunately, many animal models of cancer which introduce cancer cell lines into an animal are confounded by immune responses that are influenced by differences between the genetic background of the host animal and the cancer cell lines that are being evaluated. Specifically, in cancer models in which host animals and cancer cell lines do not share an essentially identical genetic background, there are a variety of problems including those associated with "non-self" immune responses by the host's immune system that are akin to those seen in the rejection of transplanted organs between individuals. The non-self immune responses that can result from the host immune system's recognition of non-self antigens on allogeneic cancer cells creates an immune response to these cancer cells that does not occur in human cancer patients.

As noted for example in Appellants' specification at page 17, line 12 – page 18, line 20, in order to mimic what has happened to a patient diagnosed with a cancer in animal models of cancer immunotherapy, the antigenic profile of cancer cells must mimic that of host cells. In this context, a

crucial aspect of the present invention is the characterization of the effects of SLC in an animal model where the cancer cells are syngeneic. In particular, syngeneic is known in the art to refer to an extremely close genetic similarity or identity especially with respect to antigens or immunological reactions. Syngeneic systems include for example, models in which organs and cells (e.g. cancer cells and their non-cancerous counterparts) come from the same individual, and/or models in which the organs and cells come from different individual animals that are of the same inbred strain. In contrast to syngeneic, the term allogeneic is used to connote a genetic dissimilarity between tissues or cells that is sufficient to effect some type of immunological mechanism or response to the different antigens present on the respective tissues or cells. A specific example of an allogeneic model is one in which cancer cells from one strain of mice are transplanted into a different strain of mice. Allogeneic models are particularly useful for studying transplantation immunity and for the evaluation of molecules that can suppress the immune response to non-self antigens present on the transplanted tissues.

In Example 10 at page 80, Appellants' specification teaches that SLC is observed to exhibit functional activity in a syngeneic mammalian cancer (e.g. as recited in claim 32).

B. The Art Cited By The Patent Office For Teaching SLC Activity Discloses An Immune Response In Mice Injected With Cancer Cells Having Dissimilar Histocompatibility Complex Antigens

To make the outstanding rejection, the Patent Office relies on two disclosures of SLC subject matter, WO 96/06169 and WO/038706. WO 96/06169 teaches the SLC polynucleotide and polypeptide sequences (e.g. SEQ ID NO: 1 as recited in Applicants' claims) but fails to disclose any functional data regarding SLC. WO/038706 teaches the SLC polynucleotide and polypeptide sequences as well as functional data showing that when the BDF-1 mouse strain is inoculated with either the B16 melanoma or CT26-13 colon carcinoma cell lines, an immune response to these cancer cells is observed, and further that this immune response can be modulated by SLC (Example 6 at page 35-37).

As noted above, WO/038706 describes immune responses in BDF-1 mice injected with either the B16 melanoma or CT26-13 colon carcinoma cell lines. As shown by the excerpts from

the ATCC catalog that are provided in the evidence Appendix, the B16 melanoma cell line is derived from the C57BL/6J strain of mice and the CT26-13 colon carcinoma cell line is derived from the Balb/c strain of mice. As is known in the art, the Balb/c, C57BL/6J and BDF-1 strains of mice are not genetically identical and instead exhibit distinct histocompatibility antigen expression "profiles" (i.e. the pattern of expression of the various major and minor histocompatibility complex antigens). In this context, those of skill in the art understand that a host immune response to transplanted cells having non-identical histocompatibility complex antigens is a typical and expected phenomena.

C. A Disclosure Of SLC's Activity In BDF-1 Mice Inoculated With Allogeneic Balb/C Or C57BL/6J Derived Tumor Cells Does Not Render The Activity Of SLC In Syngeneic Animals Obvious

WO/038706 teaches that an immune response is observed in BDF-1 mice inoculated with either the B16 melanoma or CT26-13 colon carcinoma cell lines and that the observed immune responses are modulated by SLC. In such situations, those of skill in the art understand that an immune response to allogeneic tissues does not reasonably predict an immune response to syngeneic tissue. Instead, skilled artisans understand that in cancer models where the host animals and cancer cell lines do not share an essentially identical genetic background, one typically observes a "non-self" immune response to the cancer cells, one that: (1) is akin to those seen in the rejection human organ transplants; and (2) is not observed in human cancers (which are syngeneic).

Skilled artisans will further note that the B16 melanoma and CT26-13 colon carcinoma cell lines are well established in culture and known to express endogenous cytokines that allow them to grow in an autocrine manner (see, e.g. Stackpole et al., In Vitro Cell Dev Biol Anim 1995, 31(3):244-251 and Shimizu et al., Cancer Res 1996, 56(14):3366-3370, references discussed in Appellants' specification at page 20, lines 1-13). Consequently, artisans will further note that any characterizations of an immune response and associated SLC activity in animals inoculated with B16 melanoma and CT26-13 colon carcinoma cell are likely to be confounded by these cell lines' production of autocrine cytokines (cytokines which can themselves modulate the host animal's immune response).

Because an immune response to allogeneic tissues does not reasonably predict an immune response to syngeneic tissues and further because the disclosure in WO/038706 teaches cancer cells

that express cytokines that can modulate an immune response independent of SLC, the disclosures of WO 96/06169 and WO/038706 are not sufficient to render the invention recited in claim 32 obvious. For this reason, the Patent Office asserts that an artisan would have been motivated to arrive at the claimed invention by combining the disclosures in WO 96/06169 or WO/038706 with selected elements found in the Kirk and Nishioka and Miller and Lode disclosures. The propriety of this combination is discussed below.

D. One of Skill In The Art Would Not Agree With The Patent Office's That the Deficiencies In WO 96/06169 and WO/038706 Are Remedied by Combining these Disclosures with the Disclosures in Kirk and Nishioka and Miller and Lode

To make the rejection under 35 U.S.C. § 103(a), the Patent Office asserts that the deficiencies in WO 96/06169 and WO/038706 are remedied by combining these disclosures with the disclosures in Kirk and Nishioka and Miller and Lode. Kirk provides a review of dendritic cell technologies and teaches that when dendritic cells transfected with cytokine genes are transplanted into mice, an immune response is observed. Nishioka discloses studies of the immunomodulatory properties of the cytokine IL-12 in a syngeneic cancer model. Miller discloses studies of the immunomodulatory properties of the cytokine IL-7 in a syngeneic cancer model. Lode discloses studies of the immunomodulatory properties of the cytokine IL-2 in a syngeneic cancer model. Kirk, Nishioka, Miller and Lode do not mention SLC anywhere in their disclosures.

The Patent Office asserts that one of skill in the art would have been motivated to arrive at the invention recited in claim 32 by combining the disclosures of WO/038706 and WO 96/06169 with those found in Kirk, Nishioka, Miller and Lode because:

> "[g]iven that WO/038706 and WO 96/06169 specifically teach that SLC is an anti-tumor immunomodulatory agent wherein the references are specifically drawn to treating cancer with said immunomodulatory agent, it is clear that the cytokines, all of which are anti-tumor immunomodulatory agents, are functional equivalents each for the other and substitution of one for the other is obvious" (page 3 of the Office Action dated September 20, 2007).

Appellants respectfully traverse this rejection because one of skill in the art would not agree with the above-quoted technical arguments that are relied upon by the Patent Office to reject claim 32 under 35 U.S.C. § 103(a). For example, a physician treating a patient suffering from melanoma

by following a therapeutic regimen that calls for IL-2[1] would not agree that he or she could simply substitute SLC and/or IL-7 and/or IL-12 for this IL-2 because, as the Patent Office asserts, they are all "functional equivalents each for the other and substitution of one for the other is obvious". In fact, a physician who used SLC, IL-2, IL-7 and IL-12 interchangeably in the various individual therapeutic protocols for which each cytokine is approved would likely have his professional competence called into question.

As noted above, those of skill in this art understand that while the highly complex mammalian immune response involves a number of different immunomodulatory cytokines including SLC, IL-2, IL-7 and IL-12, these immunomodulatory cytokines are not "functional equivalents" of each other. The artisan might emphasize this point for example by noting that the different functional roles that these cytokines play in the mammalian immune response is reflected in their very different chemical structures, structures which are reproduced below for the Board's convenience:

134 amino acid secondary lymphoid tissue chemokine polypeptide (GenBank Accession No. CAA06653):

MAQSLALSLLILVLAFGIPRTQGSDGGAQDCCLKYSQRKIPAKVVRSYRKQEPSLGCSIPAILFLPRKRSQAELCAD
PKELWVQQLMQHLDKTPSPQKPAQGCRKDRGASKTGKKGKGSKGCKRTERSQTPKGP; and

153 amino acid interleukin-2 polypeptide (GenBank Accession No. AAB46883):

MYRMQLLSCIALSLALVTNSAPTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQ
CLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT;
and

253 amino acid Interleukin-12 polypeptide (GenBank Accession No. AAD16432):

MWPPGSASQPPPSPAAATGLHPAARPVSLQCRLSMCPARSLLLVATLVLLDHLSLARNLPVATPDPGMFPCLHHSQN
LLRAVSNMLQKARQTLEFYPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSFMM
ALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFNSETVPQKSSLEEPDFYKTKIKLCI
LLHAFRIRAVTIDRVMSYLNAS

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[1] IL-2 has been approved by the U.S. Food and Drug Administration for the treatment of patients suffering from a number of cancers including malignant melanoma.

177 amino acid Interleukin-7 polypeptide (GenBank Accession No. NP_000871):

MFHVSFRYIFGLPPLILVLLPVASSDCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICDANKE
GMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQVKGRKPAALGEAQPTKSLEENKSLKEQKKLNDLC
FLKRLLQEIKTCWNKILMGTKEH

As noted for example in M.P.E.P. 2143.02, prior art can be modified or combined to reject claims as *prima facie* obvious only as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As noted in section C above, one of skill in the art would not agree with the Patent Office's belief that the observation of an immune response to allogeneic tissues provides a reasonable expectation of an immune response to syngeneic tissues. Consequently, the disclosures of WO 96/06169 or WO/038706 are not sufficient to render the invention recited in claim 32 obvious. As noted in this section, one of skill in the art would not agree with the Patent office's assertions that the deficiencies in WO 96/06169 and WO/038706 are nonetheless overcome by combining these disclosures with the disclosures in Kirk, Nishioka, Miller and Lode because SLC, IL-2, IL-7 and IL-12 are simply well known functional equivalents where "substitution of one for the other is obvious". One of skill in the art would instead note that these immunomodulatory cytokines play different roles in the immune response, and one cannot use a disclosure regarding the activity of a first cytokine (e.g. IL-2, IL-7 or IL-12) to reasonably predict the activity of a completely different cytokine (e.g. SLC).

For the reasons noted above, the disclosures of WO 96/06169 or WO/038706 in combination with the disclosures in Kirk, Nishioka, Miller and Lode cannot be used to render the invention recited in claim 32 obvious. For this reason, Applicants' attorney respectfully requests the withdrawal of the rejection under 35 U.S.C. §103.

VIII. Conclusion

In light of the above arguments, Appellants respectfully submit that the cited references do not render obvious the claimed invention. More specifically, Appellants' claim recites novel and non-obvious elements which patentably distinguish over any and all references under 35 U.S.C. §103. As a result, a decision by the Board of Patent Appeals and Interferences reversing the Examiner and directing allowance of the pending claims in the subject application is respectfully solicited.

Respectfully submitted,

GATES & COOPER LLP

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WJW/sjm

G&C 30435.152-US-I1

CLAIMS APPENDIX

1-31. (CANCELLED)

32. A method of attracting T lymphocyte or mature host dendritic cells to a site of a syngeneic tumor in a mammal comprising the steps of:

(a) obtaining dendritic cells from the mammal;

(b) introducing an exogenous polynucleotide encoding secondary lymphoid tissue chemokine as shown in SEQ ID NO: 1 into the dendritic cells so that the cells express the secondary lymphoid tissue chemokine; and

(c) placing dendritic cells generated in step (b) at the site of the syngeneic tumor in the mammal;

wherein the secondary lymphoid tissue chemokine expressed by the dendritic cells generated in step (b) attracts T lymphocyte or mature host dendritic cells to the site of the syngeneic tumor in the mammal.

EVIDENCE APPENDIX

This evidence appendix includes: (1) an ATTC product description of the B16 melanoma cell line showing that it was derived from the C57BL/6J strain of mice; and (2) an ATTC product description of the CT26 colon carcinoma line showing that it was derived from the Balb/c strain of mice.

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Organism:	Mus musculus (mouse)	**Morphology:**	Spindle
Source:	**Organ:** skin **Disease:** melanoma **Strain:** C57BL/6J		
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			Related Ce
Applications:	transfection host(technology from amaxa Roche FuGENE® Transfection Reagents)		
Tumorigenic:	Y		
Propagation:	**ATCC complete growth medium:** The base medium for this cell line is ATCC-formulate Eagle's Medium, Catalog No. 30-2002. To make the complete growth medium, add the foll the base medium: fetal bovine serum to a final concentration of 10%. **Temperature:** 37.0°C **Atmosphere:** air, 95%; carbon dioxide (CO2), 5%		
Subculturing:	**Protocol:**		

1. Remove and discard culture medium.
2. Briefly rinse the cell layer with 0.25% (w/v) Trypsin- 0.53 mM EDTA solution to serum that contains trypsin inhibitor.
3. Add 2.0 to 3.0 ml of Trypsin-EDTA solution to flask and observe cells under an inve cell layer is dispersed (usually within 5 to 15 minutes).
   Note: To avoid clumping do not agitate the cells by hitting or shaking the flask whil to detach. Cells that are difficult to detach may be placed at 37°C to facilitate disper
4. Add 6.0 to 8.0 ml of complete growth medium and aspirate cells by gently pipetting.

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Organism:	Mus musculus (mouse)	**Morphology:**	fibroblas
Source:	**Organ:** colon **Disease:** carcinoma **Strain:** BALB/c		
Cellular Products:	beta galactosidase (beta-gal) [53315]		
Permits/Forms:	In addition to the MTA mentioned above, other ATCC and/or regulatory permits may be re of this ATCC material. Anyone purchasing ATCC material is ultimately responsible for o Please click here for information regarding the specific requirements for shipment to your l		
			Related Ce
Tumorigenic:	Y		
Antigen Expression:	H-2d [53315]		
Comments:	CT26 is an N-nitroso-N-methylurethane-(NNMU) induced, undifferentiated colon carcinc cloned to generate the cell line designated CT26.WT (ATCC CRL-2638). CT26.WT was stably transduced with the retroviral vector LXSN that contains the lacZ gen tumor associated antigen (TAA), beta-galactosidase (beta-gal). [53315] The vector is driven by the Moloney murine leukemia virus (MoMuLV) long terminal repea contains a gene controlling resistance to neomycin transcribed from the SV40 promoter. The cells were grown in G418 for seven days, cloned, and evaluated for beta-gal productio The lethal subclone CT26.CL25 (ATCC CRL-2639) was selected for use in all in vitro and in of its stable high expression of both beta-gal and the class I molecule H-2 Ld. [53315] The growth rate and lethality of CT26.CL25 and CT26.WT is virtually identical despit CT26.CL25 of the model TAA, beta-galactosidase, in normal mice. [53315] The cell line can be used as a model for testing immunotherapy protocols and in studies response.		
Propagation:	**ATCC complete growth medium:** RPMI 1640 medium with 2 mM L-glutamine adjuste		

RELATED PROCEEDINGS APPENDIX

NONE